REMARKS

Status of the Claims

Claims 5, 6, 20 and 21 were pending. Claim 5 has been amended as described herein to make explicit that the dimerizing peptides are 30 amino acids or less in length, as described throughout the as-filed specification, for example, on page 3, lines 24-25 and page 4, lines 14-15.

35 U.S.C. § 112, 1st paragraph, written description

Claims 5 and 21 were rejected under 35 U.S.C. § 112, 1st paragraph as allegedly not described by the as-filed specification. (Office Action, pages 3-5). In particular, it was maintained that the specification fails to provide an adequate written description of a 10 residue long non-naturally occurring peptide. *Id.* at page 4, citing page 15, line 16 of the specification.

The pending claims are not directed to zinc finger proteins that are joined by a single linker, as discussed on page 15 of the as-filed specification. To the contrary, the claims are drawn to zinc finger proteins comprising a dimerizing peptide. The dimerizing peptide of each zinc finger proteins "links" the zinc finger proteins by peptide-peptide interaction. Thus, the as-filed specification clearly teaches that covalent linkage via a single peptide linker is distinct from the claimed complexes, which are formed via dimerization of dimerizing peptides (page 15, lines 4-5 and lines 13-15, emphasis added):

> Two or more zinc finger proteins can be linked either covalently **or** by dimerization to have a target specificity.... Linkage by dimerizing peptides has been discussed above. Covalent linkage can be accomplished using any of the following peptide linkers.

Indeed, the specification is clear that the claimed dimerizing peptides are distinct from the single linkers cited on page 15 of the specification (see, page 48, lines 4 to 9, emphasis added):

> Dimerization modules of the type reported here may be useful when designing new zinc finger proteins that recognize extended binding sites, **and such modules provide effective alternatives to covalent linkage** (Liu et al. Proc. Natl. Acad. Sci. USA 94, 5525 (1997); Kim et al., Proc. Natl. Acad. Sci.

USA 95, 2812 (1998)) **or to the use of coiled-coil dimerization domains** (Pomerantz et al., Biochemistry 37, 965 (1998)).

Moreover, with regard to dimerizing peptides, the as-filed specification clearly evinces that Applicants were in possession of dimerizing peptides of 10 amino acids length (see, e.g., page 11, lines 20-21):

> The peptide size can vary from about 2-500 amino acids, with sizes of 8-25 amino acids being preferred.

Clearly, a skilled artisan reading this passage would have no doubt that there is literal description of dimerizing peptides of 10 amino acids in length. Accordingly, withdrawal of the rejection is in order.

35 U.S.C. 103(a)

Pomerantz

The rejection of previously pending claims 5, 6 and 20 under 35 U.S.C. § 103(a) as allegedly obvious over Pomerantz (1988) *Biochemistry* 37(4):965-970 (hereinafter "Pomerantz") in view of Krylov et al. (1994) *EMBO J.* 13(12):2849-2861 (hereinafter "Krylov") was reiterated by the Examiner. (Office Action, pages 6 to 10). Pomerantz was cited for allegedly disclosing a zinc finger protein fused to a naturally occurring dimerization domain extracted from the GAL4 protein and for suggesting the use of non-naturally occurring dimerization domains. *Id.* Krylov, reference 19 of Pomerantz, was cited for demonstrating that non-naturally occurring peptide linkers could be utilized to complex zinc finger proteins. *Id.*

In response to Applicants arguments, it was asserted that Krylov uses mutant (non-naturally occurring) leucine zipper dimerization peptides to dimerize zinc finger proteins and that it would have been obvious to use Krylov's repeating peptides with zinc finger proteins as claimed. *Id.*

To reiterate, the pending claims are drawn to a complex comprising two fusion proteins. Each fusion protein comprises a zinc finger protein and a non-naturally occurring peptide linker that forms a dimer with the corresponding non-naturally occurring peptide linker on a separate fusion protein. In addition, each peptide linker is 30 or fewer amino acids in length.

As acknowledged by the Office, Pomerantz does not teach or suggest non-naturally occurring linker peptides that dimerize with each other. Nor does Pomerantz in any suggest using non-naturally occurring peptides that are less than 31 amino acids in length. Rather, at best, Pomerantz suggests that naturally occurring dimerization domains of longer length should be used (Pomerantz, page 966, left column to right column, emphasis added):

> To begin exploring the potential advantages of dimerization in the design of novel DNA-binding proteins, we south to construct a zinc finger protein that can form homodimers and heterodimers. Our approach involved structure-based fusion of zinc fingers from Zif268 to the dimerization domain of GAL4. The GAL4 domain was chosen because structural information is available for this *domain* (18) and because it contains a coiled-coil motif, a simple, well understood structure that can be further modified for design purposes. ...
>
> A DNA fragment encoding residues 2 to 59 of Zif268 [numbering scheme of Pavletich and Pabo (7)], a glycine residue, and residues 41 to 100 of GAL4 was generated by PCR and cloned ....

Therefore, GAL4 dimerization domains are described in Pomerantz are not 30 or fewer amino acids in length. Indeed, these domains are twice the size of the claimed peptides, extending from residues 41-100 of GAL4. Thus, Pomerantz does not teach or suggest the claimed complexes.

Krylov does not cure the deficiencies of Pomerantz. Krylov also fails to teach dimerizing peptides of 30 or fewer amino acids in length, choosing instead of perform experiments on mutants of an 80 amino acid leucine zipper "host" protein. See, page 2859, left column, first paragraph of Materials and methods). Krylov is clear that these 80 amino acids "contain the entire bZIP region of the protein." *Id.*

Furthermore, contrary to the Examiner's assertion, Krylov fails entirely to teach or suggest anything about zinc finger proteins complexed together via non-naturally occurring peptides fused to each of the zinc finger proteins. Rather, Krylov discloses only mutation of certain amino acid residues of naturally occurring leucine zipper domains in the context of the naturally occurring dimerization domain (Krylov, left column of page 2850 to left column of page 2851 and Fig. 1):

> The protein sequence of the first four leucine zipper heptads of the host or parent protein, the bZIP protein VBP (Iyer et al., 1991) is presented in Figure 1B.
> ....
> The lower section of Figure 1B presents the nomenclature used to describe our various mutant proteins.

Clearly, Krylov's leucine zipper dimerization mutants are not fusions as claimed. Nor do they comprise a non-naturally occurring dimerizing peptide having a length of 30 amino acids or less, as claimed.

Indeed, as noted above, the as-filed specification clearly distinguishes the claimed fusion proteins comprising non-naturally occurring dimerizing peptides from the dimerization domains disclosed in Pomerantz and Krylov (see, page 48, lines 4 to 9, emphasis added):

> Dimerization modules of the type reported here may be useful when designing new zinc finger proteins that recognize extended binding sites, and such modules provide effective alternatives to covalent linkage (Liu et al. Proc. Natl. Acad. Sci. USA 94, 5525 (1997); Kim et al., Proc. Natl. Acad. Sci. USA 95, 2812 (1998)) **or to the use of coiled-coil dimerization domains** (Pomerantz et al., Biochemistry 37, 965 (1998)).

Simply put, because each reference teaches dimerization domains of greater than 30 amino acids in length, there is no combination of Krylov and Pomerantz that would result in the claimed complexes that include peptides of 30 or fewer amino acids in length in which are selected from random peptide libraries (rather than mutating naturally occurring dimerization domains).

For all of the aforementioned reasons, the rejection of claims 5, 6 and 20 under 35 U.S.C. § 103(a) should be withdrawn.

Eisenberg

Claims 5, 6, 20 and 21 were newly rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 6,453,242 (hereinafter "Eisenberg") on the grounds that the "linkers" disclosed in Eisenberg are encompassed by the pending claims. (Office Action, pages 16-17).

In maintaining this rejection, Applicants again submit that the Examiner is misinterpreting the claims. As repeatedly noted, zinc finger proteins can be covalently linked by a single linker peptide, as described in Eisenberg (and on page 15, lines 16-20 of the as-filed specification). No dimerization is involved in this linkage, as the C-terminus of the single peptide linker is joined to one zinc finger protein and the N-terminus of the same linker is joined to another zinc finger protein, thereby creating a protein with a single linker.

However, those are not the peptide linkers of the claimed complexes. Rather, as repeatedly noted and discussed above, the pending claims are drawn to complexes comprising two fusion proteins. Each fusion protein includes a dimerizing peptide linker. As such, the claimed complexes include at least two peptide linkers (one per zinc finger protein).

Thus, Eisenberg teaches nothing about complexes containing dimerizing peptides as claimed and the rejection cannot be sustained.

35 U.S.C. 102

Claims 5, 6 and 20 were again rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,242,568 (hereinafter "Barbas") or U.S. Patent No. 6,453,242 (hereinafter "Eisenberg"). (Office Action, pages 11-16). It was alleged that because Barbas's peptides are selected, the Jun/Fos dimerization domains will also be non-naturally occurring. *Id.* e

Anticipation requires a showing that each element of the claim is necessarily present in the single reference. See, Board Decision in the instant case, page 12, citing *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 77 USPQ2d 1321, 1325 (Fed. Cir. 2005).

Here, Barbas does not disclose complexes as claimed. As a threshold matter, Applicants note that Fos/Jun dimerizing domains are greater than 30 amino acids in length. See, e.g., Appendix A: Porte et al. (1995) *J. Biol. Chem.* 270(39):22721-22730, Figure 1 and page 22723, left column):

> The Fos leucine zipper comprises residues 162-200 of c-Fos, and the Jun leucine zipper encompasses residues 277-315 of the human c-Jun protein.

On this basis alone, the rejection over Barbas cannot stand.

In addition, Barbas fails to disclose non-naturally occurring linkers. Instead, this reference discloses only the naturally occurring Fos/Jun dimerization domains (col. 28, lines 27-30 of Barbas):

> Zinc finger proteins containing from about 2 to 20 zinc fingers Zif(2) to Zif(2), and preferably from about 2 to 12 zinc fingers, may be fused to leucine zipper domains of the Jun/Fos proteins ...

The citation in Barbas to U.S. Patent No. 5,223,409 is utterly irrelevant to the instant case. This reference says nothing about mutating any dimerization domain, including Fos and/or Jun. Again, the text cited is in regards to a single linker – a single putative linker peptide selected for its ability to join two repressors. Because a single peptide linker is used, Ladner refers to this a "pseudodimer" rather than a dimer.

Likewise, the assertion that Barbas's Fos/Jun dimerizing peptides are somehow non-naturally occurring by virtue of being part of a synthetically or recombinantly produced "fusion variant" is nonsensical. Barbas says nothing about mutating Jun/Fos and, indeed, it is clear that the references teaches away from making any changes to these leucine zipper domains inasmuch as these mutations may affect dimerization. Furthermore, the claims are specific that it is the dimerizing peptide linkers themselves that are non-naturally occurring (as opposed to the Examiner's assertion that any non-naturally occurring protein will necessarily include non-naturally occurring dimerization domains).

Thus, Barbas's disclose of naturally occurring Fos/Jun dimerizing domains in the context of a recombinantly produced protein in no way anticipates the pending claims.

Similarly, Eisenberg does not disclose complexes as set forth in claims 5, 6 and 20 made up of two or more fusion proteins, each fusion protein comprising a non-naturally occurring dimerizing peptide linker. Instead, as noted above and previously, Eisenberg describes covalent linking of zinc finger proteins via a single peptide linker that joins the zinc fingers to each other. Eisenberg's single linker does not dimerize in order to join the zinc finger proteins together. Thus, Eisenberg does not disclose all the elements of the claimed complexes.

For all of the aforementioned reasons, the rejections of claims 5, 6 and 20 under 35 U.S.C. § 102(e) should be withdrawn.

CONCLUSION

Applicants believe that the claimed subject matter is now in condition for allowance and early notification to that effect is respectfully requested. If any issues remain to be addressed, the Examiner is encouraged to telephone the undersigned.

Please address all correspondence to the undersigned.

Respectfully submitted,

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